Treatment Considerations for Elderly and Frail Patients With Neuropathic Pain

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Currently, an estimated 38 million individuals 65 years or older live in the United States, and more than 11 million of these individuals are 80 years or older. Older people are at high risk of neuropathic pain because many diseases that cause neuropathic pain increase in incidence with age. Depending on their underlying health, older adults with neuropathic pain may have to cope with multiple co-existing diseases, polypharmacy, and impaired functional ability. The objective of this article is to review how aging and frailty affect the treatment of older adults with neuropathic pain. Specific topics reviewed include the complexity of treatment decisions in older patients due to aged heterogeneity, multimorbidity, and polypharmacy; selection of treatment in an effort to maximize patients' functional abilities in addition to relieving their pain; more careful dosing (usually lower) and monitoring of pharmacotherapy relative to younger patients due to age-related changes in pharmacokinetics and pharmacodynamics; and underrepresentation of older adults in clinical trials of neuropathic pain treatments, which further compromises physicians' ability to make informed treatment decisions.

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> ADL = activity of daily living; IADL = instrumental ADL; NSAID = non-steroidal anti-inflammatory drug

In the United States, 17% of the population is 60 years or older, and more than 38 million individuals are 65 years or older.[1] Furthermore, more than 11 million of these individuals are 80 years or older. This statistic is important because this group has the highest prevalence of comorbidity, disability, and frailty of any age group. Experts project that by 2030 the number of persons aged 65 years or older in the United States will increase to an estimated 71 million, and the number of persons aged 80 years or older will increase to an estimated 19.5 million.[1]

The burden of neuropathic pain, defined as pain arising as a direct consequence of a lesion or disease affecting the somatosensory system,[2] is disproportionately experienced by older patients. For example, in a multinational, cross-sectional study of patients with chronic neuropathic pain, half of all patients were 65 years or older.[3] Older adults are at increased risk of neuropathic pain compared with younger adults because many diseases that cause neuropathic pain increase in incidence with age. These age-related diseases/conditions include diabetes mellitus (painful diabetic neuropathy),[4] herpes zoster (postherpetic neuralgia),[5] low back pain (such as lumbar spinal stenosis),[6] many cancers,[7]

limb amputation,[8] and stroke.[9] Indeed, the incidences of postherpetic neuralgia, painful diabetic neuropathy, and phantom limb pain are all several times higher in patients 75 years or older than in patients between 45 and 59 years.[10] Furthermore, these and other diseases commonly coexist in older patients, which results in patients with neuropathic pain frequently having complex drug regimens that complicate pharmacotherapeutic choices.

Given the large number of older persons with neuropathic pain and their complex health problems, the objective of this article is to review how aging and frailty affect the treatment of older adults with neuropathic pain. The specific principles and topics include aged heterogeneity, multimorbidity, functional status, geriatric pharmacotherapy, and limitations in the evidence base for treatment decisions for older adults.

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AGED HETEROGENEITY

The proportion and number of older adults are substantial and increasing worldwide (Table 1). An important consideration in treating older adults is aged heterogeneity, that is, older people are the most heterogeneous of any age group on a wide variety of physical, psychological, social, and functional characteristics.[11] On one end of the spectrum of health care are people with few or no medical problems who are physically active and show minimal age-related decline in function. For them, treatment options are generally the same as for younger people. At the other end of the spectrum are frail or vulnerable individuals, who have multiple medical problems, take multiple medications, are physically inactive, and are functionally disabled. Of course, there are a large number of people between these ends of the spectrum, a state that has been called usual aging.[12] A corollary concept is that a given person's chronological age is not necessarily equal to their biological age.

Frailty is defined as a state of late life decline characterized by weakness and failure to thrive that puts individuals at high risk of adverse outcomes.[13] Frailty results from decreased physiologic reserves and multisystem dysregulation with limited capacity to maintain homeostasis and respond to stresses. Frailty is marked by loss of function and increased susceptibility to morbidity and mortality.[14,15] Clinical manifestations of frailty include alterations in mobility, strength, endurance, nutrition, and physical activity. By this definition, the prevalence of frailty in the Cardiovascular Health Study was 7% in community-dwelling participants 65 years or older and 30% in those 80 years or older.[13]

A concept related to frailty is vulnerability. The term *vulnerable elder* has been defined as people 65 years or older who are at increased risk of death or functional decline.[16] In the Assessing Care of Vulnerable Elders project,[16] investigators identified age (75-84 years and ≥85 years), self-rated health (fair or poor), limitation in physical functioning, and any functional disability as predictors of death or functional decline during a 2-year period compared with the lower-scoring majority of the sample. Using this definition, these researchers developed a set of quality measures specific for vulnerable elderly patients. An underlying theme in clinical and research work on frailty and vulnerability is that treatment decisions are considerably more complex for these individuals than for healthy older people.

Aged heterogeneity influences the effect of neuropathic pain. The effect ranges from a reduction in enjoyment of life in healthy elders to progressive functional decline, potential nursing home placement, and even death in frail or vulnerable elders. Aged heterogeneity also influences the

TABLE 1. **Number of Older Adults by Age Group for 8 Countries, 2008**

Country	Age group (y)		
	≥65	≥75	≥80
Australia	2,793,880	1,326,032	791,263
China	106,125,141	37,603,535	16,876,392
Finland	868,096	405,536	229,540
Germany	16,515,063	6,979,401	3,996,499
Italy	11,656,582	5,675,840	3,285,399
Japan	27,494,233	12,846,590	7,271,762
United Kingdom	9,735,756	4,671,190	2,755,763
United States	38,690,169	18,635,957	11,409,264

Data from US Census Bureau International Database (http://www.census.gov/ipc/www/idb/).

goals of care. For the active older person, the goals of care may be the ability to travel and lecture, whereas in the frail individual, the goals may be the ability to better transfer from bed to chair and to use an assistive device to walk. Furthermore, it informs treatment selection and potential adverse effects of treatment because healthy elders may be more likely to withstand a procedure or certain drugs compared with frail elders. Finally, it establishes who is involved in treatment decisions. Family members and caregivers become important influences on treatment selection and provision in dependent older people with neuropathic pain.

MULTIMORBIDITY

Another important consideration in treating older adults is multimorbidity, defined as the coexistence of 2 or more diseases or conditions.[17] Comorbidity is a related concept that refers to the interaction between 2 conditions or the effect one condition has on another condition. Multimorbidity is a common problem in older people because chronic diseases develop with increasing age and accumulate over time.[18] In Medicare studies in the United States, 65% of adults older than 65 years have multiple chronic diseases.[19] The percentage of people with multimorbidity increases with age even among older individuals. In a US study in general practice, the prevalence of multimorbidity was 73% in those 80 years or older,[20] whereas in a recent Australian study, the prevalence of multimorbidity was 75% for those aged 65 to 74 years and 83% for those 75 years or older.[21] The most common diseases include visual impairment (eg, macular degeneration, diabetic retinopathy, glaucoma, and cataracts), hearing impairment, cardiovascular diseases (eg, hypertension, coronary artery disease, and congestive heart failure), musculoskeletal conditions (eg, arthritis), dementia, stroke, and diabetes mellitus (Table 2). Multimorbidity is strongly associated with frequent use of health services and high expenditures[19] and is

TABLE 2. **Common Coexisting Conditions in Older Adults**

Chronic pain	Cancer
Urinary incontinence	Dementia
Falls	Parkinsonism
Influenza and pneumonia	Insomnia
Herpes zoster and postherpetic neuralgia	Chronic obstructive pulmonary disease
Urinary tract infection	Visual impairment
Hypertension	Hearing impairment
Coronary artery disease	Gastroesophageal reflux disease
Congestive heart failure	Constipation
Diabetes mellitus	Osteoarthritis
Stroke	Osteoporosis

Data from *Ann Fam Med*[20] and *Med J Aust*.[21]

also associated with neuropathic pain. In a large insurance database cohort (average age, 58 years), 70% of patients with neuropathic pain had 2 or more chronic comorbidities compared with only 13% of age- and sex-matched patients without neuropathic pain.[22]

Multimorbidity modifies the risks and benefits of neuropathic pain treatment in older patients, depending on the diseases and their interactions. Consider a patient with postherpetic neuralgia who has coexisting dementia. The assessment of pain and titration of analgesic therapy are challenging because of the effect of cognitive impairment on pain ratings. Caregiver perceptions and stress may have a major effect on treatment decisions and patient-physician interactions. Furthermore, some neuropathic pain treatments can worsen the cognitive status of the patient. Finally, some common comorbid conditions in older adults make the use of neuropathic pain drugs risky. Tricyclic antidepressants are contraindicated during the recovery phase after myocardial infarction or in patients with prolonged QT on electrocardiography. Use of anticonvulsants and antidepressants in patients with depression and suicidality has black box warnings from the Food and Drug Administration. Opioids are contraindicated in patients with ileus.

The complexity of determining the risks and benefits of treatment increases as the number of coexisting diseases increases. For example, physicians may encounter a diabetic patient with painful diabetic peripheral neuropathy who is obese and has knee and back osteoarthritis, coronary artery disease, congestive heart failure, peripheral arterial disease, and depression. Although the painful diabetic neuropathy alone can negatively affect physical activity and mood, the interaction among the patient's diseases may produce an even greater negative effect on physical activity, mood, diet and glucose control, and falls and fracture risk. (The article on disease considerations in this supplement reviews the effect of specific diseases in more detail.)

FUNCTIONAL STATUS

Maintenance of independent function and living is critically important to older people and a major goal of care. Key measures of function include basic activities of daily living (ADLs) (ie, bathing, dressing, grooming, toileting, eating, and walking)[23] and instrumental ADLs (IADLs) (ie, using the telephone, traveling, shopping, cooking, doing housework, managing medications, and managing money).[24] Other important activities include paid or unpaid (volunteer) work, leisure activities, cognitive capacity, and sleep (Table 3). The need for assistance with function is common in older adults and increases with age. In 2007, among US adults aged 65 to 74 years, 638,000 (3%) required help with ADLs and 1,221,000 (6%) required help with IADLs.[25] Among adults 75 years or older, approximately 1,855,000 (11%) required help with ADLs and 3,390,000 (20%) required help with IADLs.[25] The need for assistance among older people is higher among women, multiracial populations, and those with low income.

Neuropathic pain may have potent negative effects on ADLs.[26] In a nationally representative survey of Austrians of all ages, neuropathic pain resulted in strong restrictions on daily living in 65% of individuals.[27] In studies of acute herpetic neuralgia, which has features of nociceptive and neuropathic pain, older patients had poorer physical, emotional, social, and role functioning; reduced ability to perform basic ADLs and IADLs; and impaired energy and sleep.[28,29] A study of patients aged at least 65 years with postherpetic neuralgia found that pain interfered most with general activity, mood, sleep, and enjoyment of life.[30] In a cohort of patients with painful diabetic neuropathy (mean age, 61 years), more than 60% reported moderate or severe interference with general activity, mood, walking ability, normal work, sleep, and enjoyment of life.[31] Several studies have found that different neuropathic pain conditions are associated with reduced 36-Item Short-Form Health Survey scores relative to the general population.[32,33] Increasing pain intensity correlates with increasing negative effects on functional status,[32] although this correlation is not perfect. Older patients with modest pain ratings may

TABLE 3. **Components of Functional Status in Older Adults**

Basic activities of daily living	Instrumental activities of daily living	Other key activities
Bathing	Using telephone	Paid or unpaid (volunteer) work
Dressing	Traveling	
Grooming	Shopping	Socialization
Continence	Cooking	Leisure activities
Transferring	Housework	Community activities
Walking	Managing medications	
Eating	Managing money	Cognitive capacity
		Sleep

Data from *JAMA*[23] and *Am J Am Geriatr Soc*.[24]

have considerable decline in function, whereas others with very high pain ratings manage to function adequately. Neuropathic pain in older patients has also been shown to substantially contribute to social isolation in both patients and their spouses.[34]

Given the importance of independent functioning to older adults and the effect of neuropathic pain on functioning, an important goal of neuropathic pain treatment is improvement in functional status. Therefore, physicians should add functional status measurement at baseline and during treatment to chart progress toward that goal.[35] Standard measures of basic ADLs and IADLs may not be sufficiently sensitive to change because function is traditionally measured as independent, assistance, or dependent. Some older individuals with neuropathic pain may rate their function on a particular item as independent (eg, dressing), but the pain may increase the time and effort needed to do the task. Conversely, some older individuals may already be dependent in a task (eg, bathing), but the pain increases the time and effort of the caregiver to accomplish the task. Patient ratings of pain-related interference with ADLs may be more useful measures in some patients. The 0- to 10-point interference rating measure used in the Brief Pain Inventory is a good example of such a measure.[36]

GERIATRIC PHARMACOTHERAPY

Polypharmacy, defined as either the use of multiple medications or the use of unnecessary medications, is common in older people and increases the risk of adverse drug reactions, nonadherence, and increased cost. Older adults use a disproportionately high number of drugs compared with younger adults. Analgesic, cardiovascular, gastrointestinal, endocrine, and central nervous system drugs constitute the most prevalent therapeutic classes.[37] In national surveys of medication use among community-based individuals in the United States, 84% of patients aged 65 to 74 years and 90% of patients aged 75 to 85 years take at least 1 prescription medication,[38] more than half of US adults 57 years or older take at least 5 medications or dietary supplements,[38] and 12% of people 65 years or older take at least 10 medications.[37] The average number of drugs and the proportion of individuals taking 5 or more drugs are much higher in hospital and nursing home settings. Of patients with neuropathic pain who take prescription medications for such pain, more than one-quarter also take medications for anxiety, depression, or sleep.[3] Furthermore, older adults frequently take vitamins, minerals, and herbal preparations, which can result in potential adverse effects. Polypharmacy increases the risk of drug-drug interactions in general and with medications commonly

used to treat neuropathic pain specifically. In one sample, 4% of patients, or an estimated 2.2 million patients in the United States, were taking combinations of medications likely to cause major drug-drug interactions.[38] Web-based resources (eg, epocrates) are useful for identifying drug-drug interactions.[39]

Adverse drug events (an injury resulting from a drug) and adverse drug reactions (a subtype of adverse drug event meaning harm directly caused by a drug at usual doses) are common in older adults and are related to the number and types of drugs taken, multimorbidity, and inappropriate prescribing. In recent US studies, the rate of adverse drug events among older adults in the outpatient setting was 50 per 1000 patient-years, whereas in the nursing home setting the rate was 9.8 adverse drug events per 100 resident-months (equivalent to 1181 per 1000 patient-years or 23.6-fold higher).[40,41] The most common serious adverse drug events included bleeding due to nonsteroidal anti-inflammatory drugs (NSAIDs) and anticoagulants; hypoglycemia from insulin and oral hypoglycemics; and confusional states or delirium due to opiates, anticholinergics, benzodiazepines, antipsychotics, and anticonvulsants.[40-43] Drug-related falls and injury are less common but still serious consequences of central nervous system–active drugs. Several drugs used to treat neuropathic pain, such as opioids, tricyclic antidepressants, gabapentin, and pregabalin, are among those associated with sedation, dizziness, and falls, particularly in frail or vulnerable elderly patients. NSAIDs are commonly prescribed for pain in older adults, but no evidence supports NSAID use for neuropathic pain, and these agents may have serious cardiovascular, kidney, and hematologic adverse effects in older adults. Topical medications generally have lower risk of serious adverse effects, including the lack of central nervous system adverse effects.

Patients or physicians may attribute symptoms and signs of an adverse drug event to a preexisting disease, a new disease, or usual aging. Adverse drug events should be in the differential diagnosis of any geriatric syndrome, not only to remove the offending agent but also to avoid a prescribing cascade in which another medication is used to treat the adverse drug event when it is mistakenly diagnosed as another disease or condition.[44] Nearly three-quarters of preventable adverse drug events are due to errors in monitoring, so close follow-up of patients with new prescriptions of drugs for neuropathic pain is warranted.[45]

Aging is associated with clinically important changes in pharmacokinetics[46] (Table 4) and pharmacodynamics.[47] Drug absorption is generally unchanged, but studies of drug distribution reveal increased plasma concentration of water-soluble drugs and increased half-life of fat-soluble drugs in older adults. Age-related changes in hepatic me-

TABLE 4. **Age-Related Changes in Pharmacokinetics**

Phase	Change
Absorption	Minor changes for most drugs Decreased gastrointestinal pH, emptying
Distribution	Water-soluble drugs: decreased volume of distribution and increased plasma concentration Fat-soluble drugs: increased volume of distribution and increased half-life
Hepatic metabolism	Decreased clearance and increased half-life for drugs with oxidative metabolism or high hepatic extraction ratio
Renal excretion	Decreased clearance and increased half-life of renally eliminated drugs

Data from *Am J Geriatr Pharmacother.*[46]

tabolism lead to decreased clearance and increased half-life of drugs that undergo phase 1 oxidative metabolism or have high hepatic extraction ratios. Finally, age-related decline in kidney function leads to decreased clearance and increased half-life of drugs eliminated by the kidney. Approximately 7% of older adults aged 60 to 69 years and at least 26% of adults 70 years or older have stage III chronic kidney disease (estimated glomerular filtration rate of <60 mL/min per 1.73 m^2). Drugs used for neuropathic pain that are renally excreted include gabapentin and pregabalin; thus, dosage adjustment is necessary in patients with renal impairment.

The pharmacodynamic change of most relevance to neuropathic pain treatment involves the central nervous system. A recent comprehensive review found that older adults have increased pharmacodynamic sensitivity to central nervous system–active drugs, particularly anesthetics, benzodiazepines, and opioids.[47] This increased pharmacodynamic sensitivity combined with age-related changes in central nervous system physiologic function places the older adult at increased risk of an amplified response to central nervous system–active drugs. The implication of these age-related changes in pharmacokinetics and pharmacodynamics for the prescription of medications for neuropathic pain is that older adult patients require more careful dosing (usually lower), titration (usually slower), and monitoring compared with younger patients. The heterogeneity of older adults previously mentioned applies to drug tolerance and dosing such that some older patients will not tolerate usual adult doses but others will tolerate and need the same dosing as a younger person.

LIMITATIONS IN THE EVIDENCE BASE FOR TREATMENT OF OLDER ADULTS

Older adults are underrepresented in clinical trials in a number of therapeutic areas.[48-52] In particular, vulnerable and frail older adults are routinely excluded from clinical trials. One study of more than 16,000 patients with cancer in clinical trials found that 25% of the patients were 65 years or older and 13% were 70 years or older.[49] However, more than 60% of all cancer cases occur in individuals 65 years or older, and 47% of all cancer cases in the United States occur in individuals 70 years or older. A study of the published literature on acute coronary syndromes from January 1966 to March 2000 found that trial enrollment of patients 75 years or older increased from 2% for studies published during 1966-1990 to 9% during 1991-2000. Both percentages are well below the 37% of patients 75 years or older among all patients with myocardial infarction, leading the authors to conclude that older adults remain underrepresented in published trial literature relative to their disease prevalence.[50]

The exclusion of older adults with comorbidities and the underrepresentation of the "old old" (people >80 years) are phenomena seen in clinical trials of medications for neuropathic pain. In a study of pregabalin for painful diabetic neuropathy, patients (mean age, 60 years) were required to be generally free of serious or unstable medical conditions, psychiatric disorders, amputations other than toes, and nondiabetic neurologic disorders.[53] In a study of pregabalin for postherpetic neuralgia, patients (mean age, 73 years; age range, 36-96 years) were excluded if they had active malignant disease or any clinically important respiratory, hematologic, hepatic, or cardiovascular disease.[54] In a clinical trial of gabapentin for postherpetic neuralgia, patients (median age, 73 years; age range, 39-90 years) were excluded if they had the following: immunocompromised state, severe hepatic or renal insufficiency, serious hematologic disease, severe pain other than that caused by postherpetic neuralgia, or any serious or unstable medical condition.[55] The exclusion of older adults with comorbidities or frailty from clinical trials might relate in part to concern for the safety of these vulnerable patients. Recruitment and retention of older adults into clinical trials are also known to be problematic, and specific efforts aimed at older adults must be made to recruit a generalizable study sample.[56] Regardless of the underlying reasons, the underrepresentation of older adults reduces the generalizability of clinical trial results and interferes with our ability to estimate the benefits and risks of treatment of older individuals.

CONCLUSION

A large number of older adults are at risk of neuropathic pain because many diseases that cause neuropathic pain increase in incidence with age, such as diabetes mellitus, herpes zoster, low back pain, cancers, limb amputation, and stroke. The wide heterogeneity of health in older adults

influences the effect of neuropathic pain, assessment of pain and pain comorbidities, goals of care, and selection of treatments, particularly for frail or vulnerable elderly individuals. The complexity of determining the risks and benefits of treatment increases as the number of coexisting diseases increases in a given individual. An important goal of neuropathic pain treatment is improvement in functional status given the adverse effects of neuropathic pain on functioning in older adults. Physicians can create a successful treatment plan for neuropathic pain in older adults with careful drug selection and monitoring and with attention to comorbid conditions, concurrent medications, and age-related changes in pharmacokinetics and pharmacodynamics.

REFERENCES

1. US Census Bureau. International database. Table 094. Midyear population, by age and sex. http://www.census.gov/population/www/projections /natdet-D1A.html. Access April 1, 2009.
2. Treede RD, Jensen TS, Campbell JN, et al. Neuropathic pain: Redefinition and a grading system for clinical and research purposes. *Neurology*. 2008;70:1630-1635.
3. McDermott AM, Toelle TR, Rowbotham DJ, Schaefer CP, Dukes EM. The burden of neuropathic pain: results of a cross-sectional survey. *Eur J Pain*. 2006;10(2):127-135.
4. Schmader KE. The epidemiology and impact on quality of life of postherpetic neuralgia and painful diabetic neuropathy. *Clin J Pain*. 2002;18: 350-354.
5. Schmader K, Gnann JW Jr, Watson CP. The epidemiological, clinical and pathological rationale for the zoster vaccine. *J Infect Dis.* 2008;197: S207-S215.
6. Cummins J, Lurie JD, Tosteson TD, et al. Descriptive epidemiology and prior healthcare utilization of patients in the Spine Patient Outcomes Research Trial's (SPORT) three observational cohorts: disc herniation, spinal stenosis, and degenerative spondylolisthesis. *Spine*. 2006;31:806-814.
7. Ries LAG, Melbert D, Krapcho M, et al, eds. SEER Cancer Statistics Review, 1975-2005, National Cancer Institute. Bethesda, MD, based on November 2007 SEER data submission, posted to the SEER Web site, 2008. http://seer.cancer.gov/csr/1975_2005/index.html. Accessed January 11, 2010.
8. Dillingham TR, Pezzin LE, MacKenzie EJ. Limb amputation and limb deficiency: epidemiology and recent trends in the United States. *South Med J.* 2002;95(8):875-883.
9. Pleis JR, Lethbridge-çejku M. Summary health statistics for U.S. adults: National Health Interview Survey, 2006. *Vital Health Stat 10.* 2007 Dec;(235):1-153.
10. Hall GC, Carroll D, Parry D, McQuay HJ. Epidemiology and treatment of neuropathic pain: the UK primary care perspective. *Pain*. 2006;122(1-2):156-162.
11. Nelson EA, Dannefer D. Aged heterogeneity: fact or fiction? the fate of diversity in gerontological research. *Gerontologist*. 1992;32:17-23.
12. Rowe JW, Kahn RL. Human aging: usual and successful. *Science*. 1987;237:143-149.
13. Fried LP, Tangen CM, Walston J, et al. Frailty in older adults: evidence for a phenotype. *J Gerontol A Biol Sci Med Sci*. 2001;56:M146.
14. Fried LP, Ferrucci L, Darer J, Williamson JD, Anderson G. Untangling the concepts of disability, frailty and comorbidity: implications for improved targeting and care. *J Gerontol A Biol Sci Med Sci*. 2004;59(3):255-263.
15. Ferrucci L, Guralnik JM, Studenski S, et al; Interventions on Frailty Working Group. Designing randomized, controlled trials aimed at preventing or delaying functional decline and disability in frail older persons: a consensus report. *J Am Geriatr So*c. 2004;52:625-634.
16. Wenger NS, Shekelle PG; ACOVE Investigators. Assessing care of vulnerable elders: ACOVE project overview. *Ann Intern Med*. 2001;135: 642-646.
17. van den Akker M, Buntinx F, Roos S, et al. Problems in determining occurrence rates of multimorbidity. *J Clin Epidemiol.* 2001;54:675-679.
18. Crimmins EM. Trends in the health of the elderly. *Annu Rev Public Health*. 2004;25:79-98.
19. Wolff JL, Starfield B, Anderson G. Prevalence, expenditures, and complications of multiple chronic conditions in the elderly. *Arch Intern Med*. 2002;162:2269-2276.
20. Fortin M, Bravo G, Hudon C, et al. Prevalence of multimorbidity among adults seen in family practice. *Ann Fam Med*. 2005;3:223-228.
21. Britt HC, Harrison CM, Miller GC, Knox SA. Prevalence and patterns of multimorbidity in Australia. *Med J Aust*. 2008;189:72-77.
22. Berger A, Dukes EM, Oster G. Clinical characteristics and economic costs of patients with painful neuropathic disorders. *J Pain*. 2004;5:143-149.
23. Katz S, Ford AB, Moskowitz RW, Jackson BA, Jaffe MW. Studies of illness in the aged: the index of ADL: a standardized measure of biological and psychosocial function. *JAMA*. 1963;185:914-919.
24. Fillenbaum GG. Screening the elderly: a brief instrumental activities of daily living measure. *J Am Geriatr Soc*. 1985;33(10):698-706.
25. Adams PF, Barnes PM, Vickerie JL. Summary health statistics for the U.S. population: National Health Interview Survey, 2007. *Vital Health Stat 10*. 2008 Nov;(238):1-104.
26. Meyer-Rosberg K, Kvarnstrom A, Kinnman E, et al. Peripheral Neuropathic Pain—a multidimensional burden for patients. *Eur J Pain*. 2001; 5:379-389.
27. Gustorff B, Dorner T, Likar R, et al. Prevalence of self-reported neuropathic pain and impact on quality of life: a prospective representative survey. *Acta Anaesthesiol Scand*. 2008;52(1):132-136.
28. Katz J, Cooper EM, Walther RR, Sweeney EW, Dworkin RH. Acute pain in herpes zoster and its impact on health-related quality of life. *Clin Infect Dis*. 2004;39:342-348.
29. Schmader KE, Sloane R, Pieper C, et al. The impact of acute herpes zoster pain and discomfort on functional status and quality of life in older adults. *Clin J Pain*. 2007;23:490-497.
30. Oster G, Harding G, Dukes E, Edelsberg J, Cleary PD. Pain, medication use, and health-related quality of life in older persons with postherpetic neuralgia: results from a population-based survey. *J Pain*. 2005;6(6):356-363.
31. Gore M, Brandenburg NA, Dukes E, Hoffman DL, Tai KS, Stacey B. Pain severity in diabetic peripheral neuropathy is associated with patient functioning, symptom levels of anxiety and depression, and sleep. *J Pain Symptom Manag*e. 2005;30(4):374-385.
32. Jensen MP, Chodroff MJ, Dworkin RH. The impact of neuropathic pain on health-related quality of life: review and implications. *Neurology*. 2007;68:1178-1182.
33. O'Connor AB. Neuropathic pain: quality-of-life impact, costs and cost effectiveness of therapy. *Pharmacoeconomics*. 2009;27:95-112.
34. Sofaer-Bennett B, Walker J, Moore A, Lamberty J, Thorp T, O'Dwyer J. The social consequences for older people of neuropathic pain: a qualitative study. *Pain Med*. 2007;8(3):263-270.
35. Dworkin RH, Turk DC, Farrar JT, et al. Core outcome measures for chronic pain clinical trials: IMMPACT recommendations. *Pain*. 2005; 113:9-19.
36. Cleeland CS, Ryan KM. Pain assessment: global use of the Brief Pain Inventory. *Ann Acad Med Singapore*. 1994;23(2):129-138.
37. Kaufman DW, Kelly JP, Rosenberg L, Anderson TE, Mitchell AA. Recent patterns of medication use in the ambulatory adult population of the United States: the Slone survey. *JAMA*. 2002;287:337-344.
38. Qato DM, Alexander GC, Conti RM, Johnson M, Schumm P, Lindau ST. Use of prescription and over-the-counter medications and dietary supplements among older adults in the United States. *JAMA*. 2008;300(24):2867-2878.
39. Perkins NA, Murphy JE, Malone DC, Armstrong EP. Performance of drug-drug interaction software for personal digital assistants. *Ann Pharmacother*. 2006;40:850-855.

40. Gurwitz JH, Field TS, Harrold LR, et al. Incidence and preventability of adverse drug events among older persons in the ambulatory setting. *JAMA*. 2003;289:1107-1116.

41. Gurwitz JH, Field TS, Avorn J, et al. Incidence and preventability of adverse drug events in nursing homes. *Am J Med*. 2000;109:87-94.

42. Budnitz DS, Shehab N, Kegler SR, Richards CL. Medication use leading to emergency department visits for adverse drug events in older adults. *Ann Intern Med*. 2007;147:755-765.

43. Schmader KE, Hanlon JT, Pieper CF, et al. Effectiveness of geriatric evaluation and management on adverse drug reactions and suboptimal prescribing in the frail elderly. *Am J Med*. 2004;116:394-401.

44. Rochon PA, Gurwitz JH. Optimising drug treatment for elderly people: the prescribing cascade. *BMJ*. 1997;315:1096-1099.

45. Higashi T, Shekelle PG, Solomon DH, et al. The quality of pharmacologic care for vulnerable older patients. *Ann Intern Med*. 2004;140:714-720.

46. Cusak BJ. Pharmacokinetics in older persons. *Am J Geriatr Pharmacother*. 2004;2(4):274-302.

47. Bowie MW, Slattum PW. Pharmacodynamics in older adults: a review. *Am J Geriatr Pharmacother*. 2007;5:263-303.

48. Bugeja G, Kumar A, Banerjee AK. Exclusion of elderly people from clinical research: a descriptive study of published reports. *BMJ*. 1997;315:1059.

49. Hutchins LF, Unger JM, Crowley JJ, et al. Underrepresentation of patients 65 years of age or older in cancer-treatment trials. *N Engl J Med*. 1999;341:2061-2067.

50. Lee PY, Alexander KP, Hammill BG, Pasquali SK, Peterson ED. Representation of elderly persons and women in published randomized trials of acute coronary syndromes. *JAMA*. 2001;286:708-713.

51. Le Quintrec JL, Bussy C, Golmard JL, Hervé C, Baulon A, Piette F. Randomized controlled drug trials on very elderly subjects: descriptive and methodological analysis of trials published between 1990 and 2002 and comparison with trials on adults. *J Gerontol A Biol Med Sci*. 2005; 60(3):340-344.

52. US Government Accountability Office (GAO). Prescription Drugs: FDA Guidance and Regulations Related to Data on Elderly Persons in Clinical Drug Trials. GAO-07-47R, September 28, 2007. www.gao.gov/products/GAO-07-47R. Accessed January 11, 2010.

53. Rosenstock J, Tuchman M, LaMoreaux L, Sharma U. Pregabalin for the treatment of painful diabetic peripheral neuropathy: a double-blind, placebo-controlled trial. *Pain*. 2004;110:628-638.

54. Sabatowski R, Galvez R, Cherry DA, et al. Pregabalin reduces pain and improves sleep and mood disturbances in patients with post-herpetic neuralgia: results of a randomised, placebo-controlled clinical trial. *Pain*. 2004; 109:26-35.

55. Rowbotham M, Harden N, Stacey B, Bernstein P, Magnus-Miller L. Gabapentin for the treatment postherpetic neuralgia: a randomized controlled trial. *JAMA*. 1998;280(21):1837-1842.

56. Witham MD, McMurdo ME. How to get older people included in clinical studies. *Drugs Aging*. 2007;24:187-196.